Remarks / Arguments

Claims 1-5, 7-11, 13-17, and 19-25 are pending in the application. Claims 6, 12, and 18 have been cancelled previously. Claims 1-3, 7-9, and 13-15 have been amended in this response.

Applicants express their appreciation for the examiner's conclusion that all §112 rejections made in the previous official action have been obviated, and for the withdrawal of the rejection under §102(e) in view of Bold.

Applicants inform the examiner that the statement on page 63 of the previous response, "Fourth, the reference does not teach any of the presently-claimed compounds (contrary to the examiner's implied conclusion otherwise)" needs correction. That statement was made in the belief that the '812 reference did not disclose any compounds within the claims of the present application, and was based upon a misreading of the claim language then being employed. However, upon a more careful review of the reference and the language of the claims of the present application, it was determined that because "q" in claims 7, 8, and 9, and " q' " in claims 13, 14, and 15 were allowed to be 0, in claims 7, 8, and 9 the lower ring (containing L, A, B, D, and E) could be unsubstituted, and in claims 13, 14, and 15 the upper ring J could be unsubstituted. This resulted in these claims reading on a number of the exemplary compounds of the reference. In the present amendment, this drafting error has been corrected by deleting the possibility of q being 0 in claims 7, 8, and 9, and deleting the possibility of q' being 0 in claims 13, 14, and 15. Furthermore, the detailed review revealed that the compound of example 79B fell within claim 13 of the present application. This has been remedied in the present amendment by deleting from claim 13 the possibility for G^4 to be $-NR^3CON(R^6)_2$. Applicants apologize for any confusion caused by the above-discussed oversights.

Comment regarding the restriction requirement

In the official action, the examiner states that claims 1-5, 7-11, 13-17, and 19-25 are pending and are examined to the extent that they embrace the elected subject matter. Restriction group II was previously elected. This group related to compounds having the formulae shown in

claims 1-3, 7-9, and 13-15 wherein the pyridazine is benzo-fused to form a phthalazine, and wherein the lower ring (shown in claims 1, 7, and 13 as containing A, B, D, E, and L) is a pyridinyl or a diazine ring, plus related pharmaceutical composition and method of use claims. However, the examiner has not indicated that non-elected subject matter has been withdrawn from consideration, and has not required amendment of the claims to delete non-elected subject matter. Applicants inquire whether the examiner intends eventually to examine the claims more broadly than the elected subject matter of original restriction group II, or whether they should submit claims which have been amended to remove non-elected subject matter. For the moment, the claims have not been amended to remove non-elected subject matter, but the examiner is informed that the applicants are prepared to do so, reserving the right to file one or more continuing applications to pursue protection for such removed non-elected subject matter.

Brief comments on the present claim structure and claims

This is a complicated case, with a complicated claim structure. As explained in the summary section of the specification, this invention relates to the sum of three overlapping sets of chemical compounds, which are set forth on pages 4-15 of the specification. These three sets of compounds are the subjects of claims 1, 7, and 13 respectively. Claims 2-3, 8-9, and 14-15 are narrower definitions of the sets of compounds defined broadly by claims 1, 7, and 13 respectively. Thus, it is first necessary to consider claims 1, 7, and 13 in assessing patentability of the claimed compounds.

Claim 1 is intended to distinguish over the art primarily in its definition of the linking group Y of the structural formula, with other groups being defined broadly. Claim 7 is intended to distinguish over the art primarily in its definition of the substituents G^3 on the lower heteroaryl ring of the structural formula, which contains A, B, D, E, and L, with other groups being defined broadly. Claim 13 is intended to distinguish over the art primarily in its definition of the substituents G^4 on the upper ring of the structural formula, with other groups being defined broadly. The preceding statements are not intended to imply that patentability of the claims is to be based only on the groups Y, G^3, and G^4, however. It is always necessary to consider the claimed invention as a whole.

The applicants originally intended to require that in claims 7, 8, and 9 the lower heteroaryl ring should be substituted, and that in claims 13, 14, and 15 the upper ring J should be substituted, but through oversight allowed these groups to be unsubstituted. As explained above, this oversight has now been corrected in the present amendment, by deleting the possibility of q being 0 in claims 7, 8, and 9, and deleting the possibility of q' being 0 in claims 13, 14, and 15.

Rejections under §112, second paragraph

Claims 1-5, 7-11, 13-17, and 20-25 have been rejected under §112, second paragraph, as being indefinite.

Regarding claims 1-3, 7-9, and 13-15, the examiner comments that the Markush groups used in defining G^1, G^3, and G^4 do not employ the standard term "and" before the final moiety of the list. The recommended revisions have been made.

Regarding claims 1-3, 7-9, and 13-15, and other dependent claims, the examiner comments that in the definition of Y, the value of p is missing. Applicants respond that in each of these claims, the value of "p" is defined, and the definition is found above the definition of Y.

Regarding claims 1-3, 7-9 and 13-15, the examiner comments that the term "prodrug" is considered indefinite. This term has been removed from the last line of these claims.

Regarding claims 5, 11 (and presumably also 17), the examiner comments that the language "having a condition of tumor growth" is indefinite. The applicants respond that in the previous amendment, the conditions listed in claims 6, 12, and 18 were moved up to claims 5, 11, and 17 respectively, to provide specificity as to the conditions of abnormal angiogenesis or hyperpermiability processes. The "condition" in claims 5, 11, and 17 is any of those listed. The language is not deemed to be indefinite.

Regarding claims 6, 12 (and presumably 18), the examiner comments that the term "including" is indefinite. The examiner has overlooked the fact that these claims were cancelled in the previous amendment. The examiner should note, however, that the subject matter which originally followed "including" (both instances) in claims 6, 12, and 18 is now the subject of claims 20-25.

Rejections under §103

Requirements for a determination of obviousness

In considering the patentability of a claimed invention, the examiner must compare the prior art with the invention as a whole, as claimed. In doing this, the Graham case requires that the examiner consider the scope and content of the prior art, the differences between the prior art and the claimed subject matter, the level of ordinary skill in the art at the time the invention was made, and objective indicia of nonobviousness (if applicable).

For a prima facie obviousness rejection to be valid, the prior art plus general knowledge in the art at the time of the invention must provide a motivation for one skilled in the art to modify the prior art (or combine references) with a reasonable expectation of success, and the references must teach or suggest all the limitations of the claims. The applicant's specification cannot be a basis for motivation, because this would constitute improper "hindsight reconstruction".

Rejection under §103 in view of Bold '812

The examiner has rejected claims 1-5, 7-11, 13-17 and 19-25 under §103 as obvious in view of Bold. Applicants respond as follows.

The examiner has not focused on particular claims in making his rejection, but has operated at a high level of generality. For example, he has not considered the claims to a method of treatment separately from the claims to compounds, and has not considered any of the claims to compounds separately from each other. In operating at this high level of generality, the examiner has failed to properly analyze the patentability of the present claims in accordance US requirements, as will be discussed below.

The examiner states, "Bold et al. teaches several phthalazines with angiogenesis activity, which include compounds claimed in the instant claims. See formula I on col. 3 and note the definition of various groups. Note the definition of N-containing A-B-D-E ring corresponds to instant A-B-D-E-L ring, Q corresponds to instant G^3, G corresponds to instant Y, X corresponds to instant J. Particularly note when Y is aryl the substituents permitted includes those claimed in

the instant claims for G^4 group. See col. 4 through col. 17 for details and preferred embodiments and col. 18-34 for process of making these compounds. Also see col. 34-81 for examples of compounds made including the tables shown therein."

"The instant claims differ from the reference in requiring variously substituted compounds with substituents in the phthalazine ring, heterocyclic ring A-B-D-E-L ring, and J ring. Furthermore, claim 19 requires specific species. Bold et al. as noted in examples shown on col. 34-81 teaches variously substituted phthalazines but does not exemplify all compounds claimed."

"However, Bold et al. teaches the equivalency of exemplified substituted phthalazines shown in examples and the tables stated above with phthalazines with variously substituted in aryl ring, N-A-B-D-E ring and the aryl ring of the phthalazine ring claimed in the definition of compound of formula I. See cols. 1 through 17. Thsu, it would have been obvious to one having ordinary skill in the art at the time of the invention was made would have been to make compounds variously substituted phthalazine and aryl and N-A-B-D-E rings as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above."

"This rejection is similar to that made in the previous office action. Applicants' argument to overcome this rejection is not persuasive. Contrary to applicants' urging that instant Y, G^3 and G^4 are not obvious over the cited prior art, as noted above the definition of these groups overlap with corresponding groups recited in the said prior art and in view of the equivalency teaching the instant invention is obvious variant of the over the prior art."

The above quoted text contains several errors, but as these are not considered critical to the present discussion, they will not be discussed further here.

It seems to be the examiner's argument that 1) by its generic disclosure and examples, the '812 reference teaches phthalazines with angiogenesis-inhibiting activity, 2) the generic disclosure of the '812 reference overlaps in certain respects with the generic disclosure and claims of the present invention, which cover variously substituted phthalazines, 3) therefore, the '812 reference teaches phthalazines claimed in the present claims, 4) the '812 reference teaches the equivalency of the compounds within its generic disclosure with its exemplary compounds,

5) therefore, it would have been obvious to make the presently-claimed compounds. It is deemed that this argument is not a proper basis for the obviousness rejection, as explained below.

In order to arrive at compounds within present claim 1 starting from the Bold '812 disclosure, one must:

- select G to be a lower alkylene substituted with a group selected from the list of G^2 moieties in the present claim 1 instead of being substituted with the acyloxy or hydroxy substituents disclosed by the reference; or
- select G to be $-CH_2-O-$ but reverse its orientation from that which is shown and required by the teaching of the reference; or
- select G to be $-CH_2-S-$ or $-S-$ but oxidize the S atom to a sulfoxide or sulfone instead of leaving it unoxidized as taught in the reference.

In order to arrive at compounds within present claim 7 starting from the Bold '812 disclosure, one must:

- select as substituent Q a group selected from the list of G^3 substituents shown in the present claim 7, rather than employing a lower alkyl group as taught by the reference.

In order to arrive at compounds within present claim 13 starting from the Bold '812 disclosure, one must:

- select as a substituent on Bold's group Y a group selected from the list of G^4 substituents shown in the present claim 13, rather than employing any of the many possible substituents shown in the Bold disclosure on col. 5, line 55, through col. 6, line 33.

To arrive at presently claimed compounds starting from the generic disclosure of the '812 reference requires selecting certain moieties from the reference's disclosure and then modifying them in accordance with the requirements of the present claims. The art does not suggest making any of the above-identified modifications to the teachings of the '812 reference, in preference to any of the myriad other possible modifications which could be envisaged in view of the

complexity of the subject molecules. Accordingly, it is deemed that the examiner either has not made the required comparison of the presently claimed subject matter and the art, or to the extent he has compared the claimed subject matter and the art, he has employed "hindsight reconstruction" in reaching his conclusion of obviousness, and that the presently-claimed invention is not obvious in view of the teachings of the '812 reference. The fact that the reference teaches variously substituted phthalazines having a certain sort of activity does not suffice to make other variously substituted phthalazines obvious without some suggestion to modify the reference compounds to produce the presently claimed compounds. That suggestion is missing here.

In addition, Bold '812 indicates at col. 11, line 52, and at col. 13, line 25, that the subscript "r", indicating the number of substituents on the lower ring of the structural formula, should preferably be 0. Supporting this preference for having no substituents on the lower ring is Bold's data on columns 81 and 82, wherein IC_{50} values are shown for certain of the Bold compounds. Examples 1-4 (which are different salt forms of a compound having no substituents on the lower ring of the structural formula) are shown as having IC_{50} values between 0.1 and 0.26. Example 44F (which is basically the same compound, but with the lower ring bearing a methyl substituent) is shown as having an IC_{50} value of 0.624. Thus, Bold's data indicates that the desired activity decreases by a factor in the range of about 2 – 6 fold when the lower ring bears a substituent. This teaches away from the present claim 7, in which a substituent on the lower ring is required.

Rejection under §103 in view of Watanabe '936

The examiner has rejected claims 1-5, 7-11, 13-17 and 19-25 under §103 as obvious in view of Watanabe. Applicants respond as follows.

As with the rejection in view of Bold, the examiner has not focused on particular claims in making his rejection, but has operated at a high level of generality. For example, he has not considered the claims to a method of treatment separately from the claims to compounds, and has not considered any of the claims to compounds separately from each other. In operating at this

high level of generality, the examiner has failed to properly analyze the patentability of the present claims in accordance US requirements, as will be discussed below.

The examiner states, "Watanabe et al. teaches several fused pyridazine compounds useful for treating cGMP-PDE inhibitors for treating several heart diseases and asthma, which include compounds generically claimed in the instant claims. See formula I on page 2 and note the definition of A, X, Y, R^1 and n." This statement is deemed to be incorrect, as it is not seen that any of the compounds exemplified in the reference are within the present claims as now amended, and a broad generic teaching such as that provided in the reference does not teach particular compounds.

What the examiner possibly meant to say is that compounds within the present claims may be found within the broad generic disclosure of the reference by making appropriate selections of various moieties. However, even assuming this is true, it is not a proper basis for an obviousness rejection.

In the first paragraph of page 6 of the official action, the examiner explains that certain variables shown in the reference correspond to variables defined in the present claims and that there are certain overlaps in terminology.

In the second paragraph of page 6, he states, "The instant claims differ from the reference in requiring variously substituted compounds with substituents in the phthalazine ring, heterocyclic ring A-B-D-E-L ring, and J ring. Furthermore, claim 19 requires specific species."

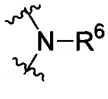
In the third paragraph he states, "Watanabe et al. as noted in examples 1-73 on pages 15-57, teaches variously substituted phthalazines but does not exemplify all compounds generically claimed."

In the fourth paragraph, the examiner states, "However, Watanabe et al. teaches the equivalency of exemplified substituted phthalazines shown in examples stated above with phthalazines with variously substituted with A, B and in the aryl ring of the phthalazine ring claimed in the definition of compound of formula I. See pages 1-6. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made would have been to make compounds variously substituted phthalazine as permitted by the reference and

expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above."

The examiner's argument with respect to Watanabe is substantially the same as that employed with respect to Bold. The applicants' response is also similar, namely, that there is no suggestion in the art to modify the teachings of the reference in such a way as to generate the compounds as presently claimed, and therefore, the rejection is not proper.

In order to arrive at compounds within present claim 1 starting from the '936 disclosure, one must:

- select "A" to be $-NR^4R^5$, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and
    - select one of R^4 and R^5 to be an optionally substituted arylalkyl group (in particular, a phenylalkyl group) or an optionally substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H, an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and
- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as " ---- " is a double bond rather than a single bond), rather than allowing X to be 

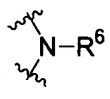
; and
- select ring "C" as a 6-membered ring, rather than a 5-membered ring; and
- select "Y" to be 

rather than 

; and
- select "B" to be an SR^{13} group or an optionally substituted heteroarylalkyl group, rather than allowing B to be H, a halogen atom, an $-NR^7R^8$ group, an $-OR^{12}$ group, an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and

- when "B" is an SR^{13} group, select the R^{13} moiety to be an optionally substituted heteroarylalkyl group, rather than H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group, and oxidize the S atom to a sulfoxide or a sulfone; and
- when "B" or R^{13} is an optionally substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms; and
- when "B" is an optionally substituted heteroarylalkyl group, select a cyano, ester, or amide substituent, rather than a hydroxyl, nitro, amino, acyl, lower alkoxy, or halogen; and select the location for one such substituent as the alkyl portion of the heteroarylalkyl group, rather than the heteroaryl portion.

In order to arrive at compounds within present claim 7 starting from the '936 disclosure, one must:

- select "A" to be $-NR^4R^5$, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and
    - select one of R^4 and R^5 to be an optionally substituted arylalkyl group (in particular, a phenylalkyl group) or an optionally substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H, an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and
- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as " ---- " is a double bond rather than a single bond), rather than allowing X to be 

; and
- select ring "C" as a 6-membered ring, rather than a 5-membered ring;

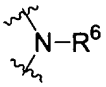
- select "Y" to be  rather than  ; and
- select "B" to be $-NR^7R^8$ or $-OR^{12}$ or SR^{13} or a manditorily substituted heteroarylalkyl group, rather than allowing B to be H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and
    - when "B" is $-NR^7R^8$, select one of R^7 and R^8 to be a manditorily substituted heteroarylalkyl group, rather than allowing R^7 and R^8 each to be H, an optionally substituted lower alkyl group, an acyl group, an optionally substituted arylalkyl group, or allowing R^7 and R^8 to be joined together to form a heterocycle; and
    - when "B" is $-OR^{12}$ or $-SR^{13}$, select R^{12} or R^{13} to be a manditorily substituted heteroarylalkyl group, rather than allowing it to be H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group; and
    - when R^7, R^8, R^{12} or R^{13} is a manditorily substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms; and
    - when "B", R^7, R^8, R^{12}, or R^{13} is a manditorily substituted heteroarylalkyl group, require at least one substituent selected from the group defined as G^3 in present claim 7 to be located on the heteroaryl portion.

In order to arrive at compounds within present claim 13 starting from the '936 disclosure, one must:

- select "A" to be $-NR^4R^5$, rather than H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted arylalkyl group, or an optionally substituted heteroarylalkyl group; and
    - select one of R^4 and R^5 to be a manditorily substituted arylalkyl group (for example, a phenylalkyl group) or a manditorily substituted heteroarylalkyl group (in particular, a pyridylalkyl group), rather than allowing R^4 and R^5 each to be H,

an optionally substituted lower alkyl group, an acyl group, or allowing R^4 and R^5 to be joined to form a heterocyclic group; and

- when R^4 or R^5 is a manditorily substituted arylalkyl or pyridylalkyl group, require at least one substituent selected from the group defined as G^4 in present claim 13 to be located on the phenyl or pyridyl portion, rather than employing any of the possible substituents listed on page 4, lines 12-15 of the reference (note that Watanabe's list of possible substituents does not overlap with the list of G^4 substituents shown in present claim 13); and

- select "X" to be a N atom which is doubly bonded in an aromatic ring (i.e., the bond shown as " ---- " is a double bond rather than a single bond), rather than allowing X to be  ; and

- select ring "C" as a 6-membered ring, rather than a 5-membered ring; and

- select "Y" to be  rather than  ; and

- select "B" to be $-NR^7R^8$ or $-OR^{12}$ or SR^{13} or an optionally substituted heteroarylalkyl group, rather than allowing "B" to be H, a halogen atom, an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted arylalkyl group; and
  - when "B" is $-NR^7R^8$, select one of R^7 and R^8 to be an optionally substituted heteroarylalkyl group, rather than allowing R^7 and R^8 each to be H, an optionally substituted lower alkyl group, an acyl group, an optionally substituted arylalkyl group, or allowing R^7 and R^8 to be joined together to form a heterocycle; and
  - when "B" is $-OR^{12}$ or $-SR^{13}$, select R^{12} or R^{13} to be an optionally substituted heteroarylalkyl group, rather than allowing it to be H, an optionally substituted lower alkyl group, an acyl group, or an optionally substituted arylalkyl group; and
  - when R^7, R^8, R^{12} or R^{13} is an optionally substituted heteroarylalkyl group, select as the heteroaryl portion a 6-membered monocyclic heteroaryl group containing at

least one N atom, rather than a 5-membered or polycyclic heteroaryl group or a heteroaryl group containing no N atoms.

The applicants maintain that in making his rejection of the claims in view of the Watanabe '936 reference, the examiner has failed to make the required comparison of the differences between the prior art and the invention as presently claimed and has failed to show a suggestion in the art sufficient to motivate one to select from the teachings of the prior art those particular definitions of variables which will generate compounds within the present claims, or to the extent he has compared the presently claimed subject matter with the art, he has used impermissible "hindsight reconstruction" in view of the applicants' own disclosure to reach his conclusion of obviousness. The discussion above relating to the many selections of variables which must be made in the generic teachings of the reference in order to derive any presently-claimed compounds, plus the lack of any suggestion in the art that the particular sets of required selections should be made, makes it clear that either the examiner did not make the requisite comparison, or that the applicants' own specification was the basis for the examiner's conclusion of obviousness. Without the present specification as a guide to the goal, there would be no way for the examiner to decide which selections of variables from the generic disclosure of the reference should be made in order to arrive at compounds within the present claims. Accordingly, it is deemed that the rejection for obviousness in view of the '936 reference is flawed and its withdrawal is requested.

Rejection of claims 2-5, 8-11, 14-17, 19, and 20-25 under §103

Respecting the rejection of claims 2, 3, 8, 9, 14, and 15 relating to compounds, the applicants argue that these should be allowable for the same reasons that the broader claims 1, 7, and 13 should be allowable, namely, that there is no suggestion in the art to modify the '812 or '936 reference in the manner required to produce the claimed compounds. Respecting claims 4, 10, and 16 relating to pharmaceutical compositions, applicants argue that these should be patentable when the claims to which they refer are found to be patentable. Respecting claims 5, 11, 17, and dependent claims 20-25 relating to methods of use, applicants argue that these should

be patentable when the claims to which they refer are found to be patentable. Regarding claim 19, applicants argue that the claimed compounds should be patentable because there is no suggestion in the art to modify the references in the manner required to produce any of the compounds listed in the claim.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

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